In The Specification:

The Paragraph beginning at page 8, line 28, is amended as follows:

Once immune cells have spread to the white matter of the central nervous system, the immune response is targeted to several different antigens on myelin. For example, there is a critical antibody response directed to myelin that activates the complement cascade with membrane attack complexes appearing in the spinal fluid. Further, T cells are targeted to certain key portions of various myelin antigens such as those presented on myelin basic protein (MBP) and proteolipid protein (PLP). The T cells in turn produce cytokines which then influence macrophages to attack the myelin and phagocytose large chunks of the myelin sheath. The concerted attack leads to areas of demyelination impairing salutary conduction along the axon and producing [[and]] the pathophysiologic defect. Multiple immune responses to several components of a supramolecular structure, like the myelin sheath in multiple sclerosis or the pyruvate dehydrogenase complex in primary biliary cirrhosis, are common in individuals with autoimmune diseases involving discrete organs.

The Paragraph beginning at page 12, line 13, is amended as follows:

In a broad sense, the immunomodulating agents of the present invention may comprise any ligand (FcR ligand) that is capable of binding to, and being internalized by, the Fc receptor of an antigen presenting cell. That is, the FcR ligand may be any protein, protein fragment, peptide or molecule that effectively binds to a Fc receptor on the surface of any antigen presenting cell. Preferably, the FcR ligand will comprise or mimic at least some portion of a constant region of an immunoglobulin molecule and will not provoke an antigenic response in the subject. In selected aspects of the invention, the FcR ligand will comprise part or all of a constant region from an IgG molecule. Particularly preferred embodiments will employ FcR ligands comprising the entire constant region of a selected immunoglobulin molecule from the species to be treated. Of course, it will also be appreciated that binding to the Fc receptor may also be a[[e]]ffected by ligands that comprise small fragments of a single constant region domain[[s]] or non amino acid based

molecular entities. In any case, the FcR ligand may be derived using modern pharmaceutical techniques such as directed evolution, combinatorial chemistry or rational drug design.

The Paragraph beginning at page 16, line 8, is amended as follows:

In any event the use of FcR mediated uptake of the immunomodulating agent avoids many of the problems associated with prior art compositions. More specifically, the methods of the present invention overcome many of the limitations associated with the administration of free peptide antagonists as disclosed in the prior art. Accordingly, efficient endocytic presentation of an immunosuppressive factor such as a TCR antagonist can generate significant levels of MHC-antagonist ligands to oppose naturally occurring MHC-autoantigenic complexes that are generated in spontaneous immune disorders involving the continuous presentation of an autoreactive antigen. Similarly, the efficient uptake of FcR ligand-agonist (or autoantigenic polypeptide) constructs and subsequent presentation of the desired agonist(s) may induce anergy in autoreactive T cells. As such, the invention may be used to treat any immune disorder that responds to the presentation of immunosuppressive factors. This is particularly true of T cell mediated autoimmune disorders including, for example, multiple sclerosis, lupu[[i]]s, rheumatoid arthritis, scleroderma, insulin-dependent diabetes and ulcerative colitis. In a like manner, the present invention can be used to selectively down-regulate the immune system with respect to continuously presented agonists such as allergens. Further, the compounds and associated compositions of the present invention may be used to selectively suppress various components of the immune system to reduce the likelihood of tissue or organ rejection following transplant.

The Paragraph beginning at page 25, line 29, is amended as follows:

Particularly preferred embodiments of the instant invention will employ recombinant nucleotide constructs to code for immunomodulating agents comprising a single fusion polypeptide. Those skilled in the art will appreciate that standard genetic engineering

technology can provide fusion proteins or chimeras that will comprise at least one FcR ligand and at least one immunosuppressive factor. As used herein the terms "chimera" or "chimeric" will be used in their broadest sense to encompass any polynucleotide or polypeptide comprising sequence fragments from more than one source. For example, a genetically engineered polypeptide incorporating a peptide TCR antagonist and a single Fc domain from an IgG molecule could properly be termed a chimeric or fusion protein. Similarly, a chimeric antibody may comprise a recombinant heavy chain[[s]] engineered to incorporate a heterologous peptide immunosuppressive factor and a wild type light chain[[s]]. For the purposes of the present invention, it is not necessary that the disparate regions be derived from different species. That is, a chimeric antibody may comprise human light and heavy chains and an engineered human TCR antagonist expressed in a CDR. Conversely, chimeric immunomodulating agents may comprise FcR ligands and immunosuppressive factors derived from different species such a human and mouse.

The Paragraph beginning at page 31, line 5, is amended as follows:

In this respect, a further aspect of the invention comprises a method for treating an immune disorder comprising administering to a patient a therapeutically effective amount of a pharmaceutical composition comprising an immunomodulating agent in combination with a physiologically acceptable carrier or diluent wherein said immunomodulating agent comprises at least one Fc receptor ligand and at least one immunosuppressive factor. For this aspect, the immunosuppressive factor may comprise a T cell receptor antagonist or agonist and the Fc receptor ligand may comprise at least part of a immunoglobulin constant region domain. As previously alluded to, the immunomodulating agent will preferably be in the form of a recombinant polypeptide or a chimeric antibody. The methods may be used to treat immune disorders comprising autoimmune disorders, allergic responses and transplant rejection and are particularly useful in treating autoimmune disorders selected from the group consisting of multiple sclerosis, lupu[[i]]s, rheumatoid arthritis, scleroderma, insulin-dependent diabetes and ulcerative colitis.

The Paragraph beginning at page 34, line 26, is amended as follows:

Alternatively, efficient FcR mediated presentation of agonists may be used to down-regulate the immune response of a mammal in accordance with the teachings herein. In this regard, the ultimately presented agonist(s) may be administered directly as the immunosuppressive factor or may be derived from autoantigenic polypeptide immunosuppressive factors which are endocytically proteolyzed. While not wishing to be bound to any particular theory, it is believed that the autoantigenic agonists may be presented by nonprofessional and/or non-activated APCs lacking costimulatory molecules. As discussed above it was surprisingly found that this type of presentation ultimately induces the inactivation of T cells. In such embodiments it is preferable that the immunomodulating agent constructs are administered in vehicles which do not contain an adjuvant so as to minimize or eliminate the activation and/or production of costimulatory molecules. Particularly preferred embodiments of this aspect of the present invention may encompass immunosuppressive factors comprising one or more autoantigenic polypeptides or fragments thereof. For example, constructs in accordance with this embodiment may comprise a fusion or chimeric IgG wherein at least one of the CDR regions has been at least partially replaced with a peptide agonist derived from PLP. Such constructs, when administered in therapeutically effective amounts in an adjuvant free pharmaceutically effective carrier should be able to alleviate at least some symptoms associated with multiple sclerosis. Other effective constructs for the treatment of multiple sclerosis may include fusion polypeptides comprising the Fc region of an IgG covalently linked to a immunosuppressive factor comprising the autoantigenic proteins MBP and PLP. These constructs would again be administered in adjuvant free carriers.

The Paragraph beginning at page 61, line 13, is amended as follows:

The administered Ig-PLP1 was efficiently presented by neonatal APCs. Both thymic (17A) and splenic (17B) APCs from neonate recipients of IG-PLP1 activated a T cell hybridoma specific for PLP1 peptide without addition of ex[[r]]ogenous antigen. APCs from neonate recipients of Ig-W were unable to activate the T cell hybridoma.

The Paragraph beginning at page 61, line 24, is amended as follows:

Neonates were injected intraperitoneal (i.p.)within 24 hours of birth with 100 μg Ig-PLPI or Ig-W in saline. When the mice reached 7 weeks of age they were immunized with 100 μg free PLP1 peptide in 200 μl CFA/PBS (1vol/1vol) s.c. in the foot pads and at the base of the limbs and tail. Ten days later the mice were sacrificed, and (18A) the lymph node (0.4 x 10^6 cells/well) and (18B) the splenic (1 X 10^6 cells/well) cells were in vitro stimulated for four days with 15ug/ml free PLP1 or PLP2, a negative control peptide corresponding to the encephalitogenic sequence 178-191 of PLP (13). One μCi/well of[^{3}H]thymidine was added during the last 14.5 hours of stimulation, and proliferation was measured using an Inotech β-counter and the trace 96 Inotech program. The indicated cpms represent the mean ± SD of triplicate wells for individually tested mice. The mean cpm ± SD of lymph node proliferative response of all mice recipient of Ig-PLP1 and Ig-W was 34,812 ± 7,508 and 37,026 ± 10,133, respectively. The mean splenic proliferative response was 3,300 ± 3,400 for the Ig-PLP1 recipient group and 14,892 ± 4,769 for the Ig-W recipient group.

The Paragraph beginning at page 63, line 13, is amended as follows:

In the spleen, ~~while~~cells from mice inoculated with Ig-W produced IL-2 and INFγ. Conversely, cells from mice injected with Ig-PLP1 produced IL-2 but failed to produce detectable levels of INFγ. The negative control, PLP2 peptide, failed to induce cytokine production.

The Paragraph beginning at page 64, line 1, is amended as follows:

Surprisingly, addition of e[[r]]xogenous INFγ to splenic cells from the mice recipient of Ig-PLP1 at birth restored the proliferative response. IL-12, an inducer of INFγ (14), also restored the splenic proliferative response.